FORM PTO-1390 (REV 11-2000) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

ATTORNEY'S DOCKET NUMBER: 246152015300

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. § 371

U.S. APPLICATION NO. (If known, see 37 CFR 1.5): 09/937834

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/EP00/02917	3/4/2000	1/4/1999

TITLE OF INVENTION: **AGGLOMERATES BY CRYSTALLISATION**

APPLICANT(S) FOR DO/EO/US: **Johannes BOOIJ; Ageeth Geertruida LEFFERTS**

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☐ This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include items (5), (6), (9) and (21) indicated below.
4. ☐ The US has been elected by the expiration of 19 months from the priority date (PCT Article 31).
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. ☒ is attached hereto (required only if not communicated by the International Bureau).
   b. ☐ has been communicated by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ An English language translation of the International Application under PCT Article 19 (35 U.S.C. 371(c)(2)).
   a. ☐ is attached hereto.
   b. ☐ has been previously submitted under 35 U.S.C. 154(d)(4).
7. ☐ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3)).
   a. ☐ are attached hereto (required only if not communicated by the International Bureau).
   b. ☐ have been communicated by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☐ have not been made and will not be made.
8. ☐ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☐ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. ☐ An English language translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern document(s) or information included:

11. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. ☒ A FIRST preliminary amendment.
14. ☐ A SECOND or SUBSEQUENT preliminary amendment.
15. ☐ A substitute specification.
16. ☐ A change of power of attorney and/or address letter.
17. ☐ A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821 - 1.825.
18. ☐ A second copy of the published international application under 35 U.S.C. 154(d)(4).
19. ☐ A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).
20. ☐ Other items or information: *; return receipt postcard.

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Express Mail Label No.: EL 736718720 US Date of Deposit: September 28, 2001

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Tami M. Procopio

sd-59393

U.S. APPLICATION NO. (if known, see 37 CFR 1.5)	INTERNATIONAL APPLICATION NO. PCT/EP00/02917	ATTORNEY'S DOCKET NUMBER: 246152015300
09/937834		

21. ☒ The following fees are submitted:

BASIC NATIONAL FEE (37 CFR 1.492(a)(1)-(5)):

	CALCULATIONS PTO USE ONLY
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO.....$1,000.00	
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO.....$860.00	
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO.....$710.00	
International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provision of PCT Article 33(1)-(4) $690.00	
International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4) $100.00	
ENTER APPROPRIATE BASIC FEE AMOUNT =	$860.00
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☒ 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	$130.00

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE	$*
Total claims	25- 20 =	5	5x $18.00	$90.00
Independent claims	1 - 3 =	0	x $80.00	$*
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ $270.00	$*
TOTAL OF ABOVE CALCULATIONS =				$1080.00
☐ Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by ½.				$
SUBTOTAL =				$1080.00
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(f)). +				$*
TOTAL NATIONAL FEE =				$*
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00 per property** +				$*
TOTAL FEES ENCLOSED =				$1080.00
			Amount to be refunded:	$*
			charged:	$1080.00

a. ☐ A check in the amount of $* to cover the above fees is enclosed.

b. ☒ Please charge my **Deposit Account No. 03-1952** in the amount of $1080.00 to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees that may be required, or credit any overpayment to **Deposit Account No. 03-1952**. A duplicate copy of this sheet is enclosed.

d. ☐ Fees are to be charged to a credit card. **WARNING:** Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

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SIGNATURE

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PATENT

Docket No. 246152015300

CERTIFICATE OF MAILING BY "EXPRESS MAIL"

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Tami M. Procopio

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In the application of:

Johannes BOOIJ
and Ageeth Geertruida Lefferts

Serial No.: Not yet assigned
Based on PCT Int'l App.: PCT/EP00/02917

Filing Date: Even date herewith

For: AGGLOMERATES BY CRYSTALLISATION

Examiner: To be assigned

Group Art Unit: To be assigned

PRELIMINARY AMENDMENT

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

Prior to examination of the above-referenced application, please amend the claims as follows:

Enclosed is the following Exhibit A:

Exhibit A: Marked-up Version of Amendments to the Claims.

AMENDMENT

Please replace presently pending claims 1-24 with the following claims 1-24:

1. Agglomerates in crystalline form comprising one or more β-lactam compounds, wherein at least one β-lactam compound has a high water affinity, and optionally containing one or more excipients, with the proviso that the rosette-like crystalline form of potassium clavulanate is excluded.

2. Agglomerates according to claim 1, wherein the agglomerates are substantially free from non-agglomerated β-lactam crystals.

3. (Amended) Agglomerates according to claim 1, wherein at least one β-lactam compound is clavulanic acid.

4. (Amended) Agglomerates according to claim 1, wherein the β-lactam compound is potassium clavulanate.

5. Agglomerates according to claim 4, consisting of only potassium clavulanate.

6. Agglomerates according to claim 4 further comprising amoxicillin.

7. (Amended) Agglomerates according to claim 1, wherein the one or more excipients are selected from the group consisting of microcrystalline cellulose and silica.

8. (Amended) Agglomerates according to claim 1, wherein the agglomerates have an average particle size between about 1 μm and 1500 μm.

9. (Amended) Agglomerates according to claim 1 in sterile form.

10. (Amended) A process for the preparing the crystallised agglomerates of claim 1, which comprises stirring at least one β-lactam in a liquid phase.

11. (Amended) A process according to claim 10, wherein the liquid phase comprises a solvent or in a mixture of solvents together with one or more anti-solvents.

12. (Amended) A process according to claim 11, wherein the ratio of the weight of the solvent containing β-lactam to the anti-solvent is about 0.05 to 10 wt.%.

13. (Amended) A process according to claim 11, wherein the solvent is selected from the group consisting of water, alcohol, ketone and ester or a mixture thereof, wherein water is present in said mixture.

14. (Amended) A process according to claim 10, wherein the anti-solvent is a ketone, an ester, or an alcohol, or a mixture of these anti-solvents, optionally containing water.

Please cancel claim 15.

16. (Amended) A process according to claim 10, wherein the stirring is performed by applying stirring devices in one or more vessels, in-line mixers or a combination thereof.

17. (Amended) A process according to claim 16, wherein the stirring device is a high shear mixer.

18. (Amended) A process according to claim 25, wherein said stirring is performed by combining and permuting different stirring devices, the speeds of said devices, the type and amount of the solvents used, and mixing one or more solvents and anti-solvents.

19. (Amended) A process according to claim 18, wherein the agglomerates have various particle sizes.

20. (Amended) A process according to claim 11, wherein the process comprises dissolving one or more β-lactams in a solvent, adjusting the pH to about neutral and mixing with the anti-solvent.

21. (Amended) A pharmaceutical formulation comprising the agglomerates of claim 1 and one or more pharmaceutically acceptable excipients.

22. (Amended) A pharmaceutical formulation comprising the crystalline agglomerates of potassium clavulanate of claim 5, amoxicillin and optionally one or more pharmaceutically acceptable inert excipients.

23. (Amended) The pharmaceutical formulation of claim 22 which contains one or more pharmaceutically acceptable inert excipients selected from the group consisting of microcrystalline cellulose and silica.

24. (Amended) A pharmaceutical dosage form comprising a pharmaceutical formulation of claim 21.

Please add the following claims 25-26:

25. (New) A process according to claim 16, wherein the liquid phase comprises a solvent or in a mixture of solvents together with one or more anti-solvents.

26. (New) A pharmaceutical dosage form comprising a pharmaceutical formulation of claim 22.

REMARKS

This application is the national phase filing of PCT application PCT/EP00/02917. The claims have been amended to eliminate multiple dependencies, provide antecedent basis for terms in dependent claims, and to conform to U.S. practice. The scope of the claims is believed unchanged.

No new matter has been added and entry of the amendment is respectfully requested.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket No. 246152015300. However, the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Respectfully submitted,

Dated: September 28, 2001

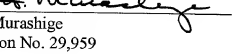
By: 

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EXHIBIT A. - VERSION WITH MARKINGS TO SHOW CHANGES MADE

1. Agglomerates in crystalline form comprising one or more β-lactam compounds, wherein at least one β-lactam compound has a high water affinity, and optionally containing one or more excipients, with the proviso that the rosette-like crystalline form of potassium clavulanate is excluded.

2. Agglomerates according to claim 1, wherein the agglomerates are substantially free from non-agglomerated β-lactam crystals.

3. (Amended) Agglomerates according to claim 1[or 2], wherein at least one β-lactam compound is clavulanic acid.

4. (Amended) Agglomerates according to [any one of the claims 1-3] claim 1, wherein the β-lactam compound is potassium clavulanate.

5. Agglomerates according to claim 4, consisting of only potassium clavulanate.

6. Agglomerates according to claim 4 further comprising amoxicillin.

7. (Amended) Agglomerates according to [anyone of the claims 1-4 or 6] claim 1, wherein the one or more excipients are selected from the group consisting of microcrystalline cellulose[, preferably Avicel®, or] and silica[, preferably Syloid® or Aerosil®].

8. (Amended) Agglomerates according to [anyone of the claims 1-7] claim 1, wherein the agglomerates have an average particle size between about 1 μm and 1500 μm[, preferably between about 500 μm and 1500 μm, more preferably between 800 μm and 1200 μm, or preferably between 1 μm and 300 μm, more preferably between 1 μm and 200 μm].

9. (Amended) Agglomerates according to [anyone of the claims 1-8] claim 1 in sterile form.

10. (Amended) A process for the [preparation of] preparing the crystallised agglomerates [as defined in anyone of the claims 1-9] of claim 1, [wherein the agglomerates are produced in a liquid phase by applying] which comprises stirring at least one β-lactam in a liquid phase [devices].

11. (Amended) A process according to claim 10, wherein the liquid phase [comprises a solution or suspension of at least one corresponding β-lactam compound in] comprises a solvent or in a mixture of solvents together with one or more anti-solvents.

12. (Amended) A process according to claim 11, wherein the ratio of the weight of the [solution] solvent containing β-lactam [compound] to the anti-solvent is about 0.05 to 10 wt.%.

13. (Amended) A process according to claim 11[or 12], wherein the solvent is selected from the group consisting of water, an alcohol, a ketone and an ester [or a] and mixtures thereof, [whereby] wherein water is present in said mixture.

14. (Amended) A process according to [anyone of the claims 10-13] claim 10, wherein the anti-solvent is a ketone, [like acetone, methylethylketone, methylisobutylketone or] an ester, [like methyl acetate, ethyl acetate, isopropyl acetate, butyl acetate] or an alcohol, [like 1-propanol, 1-butanol, 2-butanol, 2-methyl-1-propanol] or a mixture of these anti-solvents, optionally containing water.

16. (Amended) A process according to claim [15] 10, wherein the [process] stirring is performed by applying stirring devices in one or more vessels, in-line mixers or a combination thereof.

17. (Amended) A process according to claim [15 or] 16, wherein [a high shear mixer is used as] the stirring device is a high shear mixer.

18. (Amended) A process according to [anyone of the claims 10-17] claim 25, [characterised by the preparation of agglomerates with various particle sizes, by further using a] wherein said stirring is performed by combining and permuting [combination and permutation of] different stirring devices, [and their] the speeds of said devices, the type and amount of the solvents used, and [the way of] mixing [of] one or more solvents and anti-solvents.

19. (Amended) A process according to claim 18, [characterised by the preparation of] wherein the agglomerates [with] have various particle sizes[, by further using a nozzle-sprayer for the solution].

20. (Amended) A process according to [any one of the claims 10-19] claim 11, [characterised by] wherein the process comprises dissolving one or more [corresponding] β-lactams in a solvent, adjusting the pH to about neutral and mixing with the anti-solvent.

21. (Amended) A pharmaceutical formulation comprising the agglomerates of [anyone of the claims 1-9] claim 1 and one or more pharmaceutically acceptable excipients.

22. (Amended) A pharmaceutical formulation comprising [amoxicillin, preferably amoxicillin trihydrate and] the crystalline agglomerates of potassium clavulanate [as defined in] of claim 5, amoxicillin and optionally one or more pharmaceutically acceptable inert excipients.

23. (Amended) [A] The pharmaceutical formulation[, comprising a mixture of amoxicillin trihydrate and crystalline agglomerates of potassium clavulanate and one or more] of claim 22 which contains one or more pharmaceutically acceptable inert excipients [as defined in claim 4] selected from the group consisting of microcrystalline cellulose and silica.

24. (Amended) [Pharmaceutical] A pharmaceutical dosage form comprising a pharmaceutical formulation of [anyone of the claims 21-23] claim 21.

AGGLOMERATES BY CRYSTALLISATION

Field of the invention

The present invention describes agglomerates of ß-lactam compounds in crystalline form and a process to prepare the same.

Background of the invention

β-Lactam antibiotics constitute the most important group of antibiotic compounds, with a long history of clinical use. Among this group, the prominent ones are the penicillins and cephalosporins.

Presently, most of the β-lactam antibiotics used are prepared by semi-synthetic methods. These β-lactam antibiotics are obtained by modifying a β-lactam product obtained by fermentation by one or more reactions.

Clavulanic acid and its alkaline metal salts and esters, another type of ß-lactam compound than the penicillin and cephalosporin, act as β-lactamase inhibitors, able to enhance the effectiveness of penicillins and cephalosporins. Clavulanic acid has been applied therefore in pharmaceutical compositions to prevent inactivation of β-lactam antibiotics. For example, the antibacterial activity profile of amoxicillin is enhanced by the use of potassium clavulanate as β-lactamase inhibitor. A combination preparation of amoxicillin trihydrate with potassium clavulanate (Augmentin®) is well known.

It is generally known that antibiotic compounds in powder form are not suitable for formulation purposes, because generally these powders perform badly as far as flowability is concerned which causes problems in the manufacturing of final dosage forms, such as tablets. Accurate dosing of the several ingredients is needed to ensure constant end product quality. In case of poor flowabilities, such accurate dosing is difficult to guarantee. Also, the needle shaped crystals, such as of potassium clavulanate, often show a low

bulk density. Thus, the contribution of such crystals to the overall volume of the final dosage form is relatively high.

To overcome these problems, often granules of compounds, for example potassium clavulanate with excipients (such as microcrystalline cellulose like Avicel® or silica like Syloid® or Aerosil®) or granules of composition, for example potassium clavulanate with other active ingredients like amoxicillin trihydrate are made before producing the final formulation. Several processes are known to form such granules. For example, in case of wet granulation, potassium clavulanate can be mixed with, for instance, amoxicillin and a binding agent after which the mixture is moistened by a solvent, granulated and bounded. Before tabletting the granules with excipients, the granulates might be sieved. This wet granulation process is economically unattractive, as it uses solvents which must be recovered and/or recycled. It is labour intensive, expensive and time consuming due to the large number of processing steps such as mixing, granulating, sieving, drying etc. Moreover, in case of unstable ß-lactam compounds such as potassium clavulanate, wet granulation is problematic due to the use of a solvent and high temperature during the drying step of the process.

Another method to granulate poor flowing powders is dry granulation. As an example, the slugging process can be mentioned as described in International patent applications WO 9116893 and WO 9219227. Here, tablets of the poor flowing material with excipients are made and subsequently broken again and sieved to produce granules. Another example of dry granulation is the compaction process as described in International patent application WO 9528927. In this application, a process has been mentioned wherein compacted granules of a ß-lactam antibiotic, for example amoxicillin, and a mixture of an active ß-lactam antibiotic and a secondary pharmaceutically active agent, for example potassium clavulanate with excipients are made using roller compacting. Subsequently, the roller compacted flakes are milled, resulting in granules which can be mixed with excipients to press the final tablets. An advantage compared to the wet

granulation is the absence of solvents. However, the dry granulation is relatively time consuming due to a large number of processing steps. Also, in case of unstable products, a quality risk exists due to locally high temperatures in the process, e.g. due to abrasion. In case the material is hygroscopic, such as potassium clavulanate, another disadvantage is the handling of the dried crystals before and during the granulation process. During this handling, the product might attract water leading to unwanted degradation reactions. Also a major disadvantage of roller compacted products is the relatively large amount of fines which should be removed using sieving techniques to improve the flowability of such products.

Furthermore, difficulties one may encounter by using dry granulation are:
- a lot of dust is produced during the slugging or roller compaction process and in some cases, for example such as amoxicillin, this dust sticks to the coarser particles and can not be separated by currently applied vibrating sieves,
- dust may deteriorate the flow properties of agglomerates,
- dust is also responsible for air born ß-lactam antibiotics particles which can cause allergic reaction.

Granules of the active ingredient in the presence of excipients are produced by the process mentioned above. It would be advantageous to have the possibility to produce granules of the pure active ingredient. In that case, the production process can be more flexible and possibly overall less excipients are necessary. Also the production of final dosage forms will be more flexible. In case of hygroscopic substances such as potassium clavulanate, however, it will be difficult to granulate using one of the above processes without the presence of excipients like microcrystalline cellulose or silica, as the latter are known to protect the hygroscopic potassium clavulanate by removing the free water from it and, thus, keeping the water activity of such compositions low. However, in the International patent application WO 9733564 a method has been mentioned in which granules of a pure active ingredient, without the presence of excipients, are made by

extrusion. Here, a paste is made of the crystalline powder by adding a liquid wherein the powder is insoluble or slightly soluble. The paste is needed then and extruded in a double screwed extruder, after which the granules are dried. The process again is not suitable for unstable products, as locally the temperature in the extruder is high (up to 80°C). Also, this wet material should be dried at elevated temperatures.

Another method to improve the flowability of needle shaped crystals, especially in the case of potassium clavulanate, is to agglomerate them during crystallisation to the so-called rosette form as described in European patent EP 277008 B1. In this case, a plurality of needle crystals radiate out from a common nucleation point. The rosettes show an increased flowability compared to the needles. However, a large disadvantage of these types of granules is the inclusion of impurities, leading to a decreased chemical quality of the product. Also, the included impurities probably increase the degradation rate of the ß-lactam compound, thus resulting in an even worse chemical quality during storage.

The object of the invention is to provide a valuable form of a ß-lactam antibiotic compound and a process to prepare such a compound that overcomes most of the above mentioned disadvantages.

Surprisingly, it has been found that novel agglomerates in crystalline form of ß-lactam antibiotics in a liquid phase are produced through a crystallisation process when a solution of at least one ß-lactam compound in a solvent or in a mixture of solvents under stirring is mixed together with one or more anti-solvents. Preferably, one or both solutions contain water.

Description of the Figure

An Electron-microscope photo of potassium clavulanate agglomerates as prepared according to Example 9 is shown in the Figure.

Summary of the invention

The present invention provides agglomerates in crystalline form comprising one or more ß-lactam compounds having at least one ß-lactam compound of a high water affinity, and optionally contain one or more excipients. Preferably, said agglomerates comprise clavulanic acid or a pharmaceutically acceptable salt thereof like potassium clavulanate. Further, the agglomerates comprising potassium clavulanate may contain amoxicillin as the active ß-lactam antibiotic compound. The term agglomerate refers to clustering of the crystals of a compound.

The excipients are microcrystalline cellulose, preferably Avicel®, or silica, preferably Syloid® or Aerosil®.

The said agglomerates can also be of sterile form.

The new agglomerates are of an average particle size between about 1 µm and 1500 µm, preferably between about 500 µm and 1500 µm, more preferably between 800 µm and 1200 µm, or between 1 µm and 300 µm, preferably between 1 µm and 200 µm.

Moreover, the agglomerates of the present invention are substantially free from non-agglomerated ß-lactam crystals, for instance, non-agglomerated crystals having a weight percentage between 0-10%.

Furthermore, a process to prepare said agglomerates has been provided for. The agglomerates are produced in a liquid phase medium, which process involves mixing together a solution or suspension of at least one ß-lactam compound corresponding to the ß-lactam compound to be prepared in agglomerate form in a solvent or in a mixture of solvents under stirring with one or more anti-solvents, whereby at least one of both solvents and co-solvent contains water. The overall weight ratio of the solution containing the ß-lactam compound to anti-solvent is about 0.05 to 10%. The solvent is for instance water or ethanol and the anti-solvent a ketone, like acetone, methylethylketone, methylisobutylketone or an ester, like methyl acetate, ethyl acetate, isopropyl acetate, butyl acetate or an alcohol, like 1-propanol,

1-butanol, 2-butanol, 2-methyl-1-propanol or a mixture of these solvents. The pH of the solution of the ß-lactam compound may be adjusted to neutral. Preferably, the solvent is water or ethanol and the anti-solvent is acetone or ethyl acetate with some water present in at least the solvent or the anti-solvent. It is possible also to add other ingredients in one of the streams (solvent, anti-solvent or mixture thereof), either suspended or dissolved.

During the preparation of the agglomerates, one or more stirring devices are used to crystallise, agglomerate and deagglomerate, or to crystallise and agglomerate, or to crystallise and deagglomerate the ß-lactam compound and optionally classification and blending with excipients and/or another ß-lactam compound in a batch or continuous operation in one or more reaction vessels or in one integrated step. Furthermore, the operation is performed by applying stirring devices in one or more vessels, in-line mixers or a combination thereof. Furthermore, it is possible to use a high shear mixer during the preparation of these agglomerates. Also, agglomerates with various particle sizes can be prepared by using a nozzle-sprayer for the ß-lactam containing solution.

The agglomerates of various particle sizes are regulated by further using a combination and permutation of different stirring devices and their speed, the type and amount of the solvents used and the way of mixing of the solvents.

Agglomerates of potassium clavulanate of the present invention show a good level of stability and hygroscopicity.

The agglomerates, prepared according to the present invention, with one or more pharmaceutical acceptable excipients are suitable for pharmaceutical formulations.

Pharmaceutical formulations comprising amoxicillin, preferably amoxicillin trihydrate and the crystalline agglomerates of potassium clavulanate of the present invention and optionally one or more pharmaceutically acceptable inert excipients form another aspect of the present invention.

Also, a pharmaceutical formulation, comprising crystalline agglomerates of amoxicillin trihydrate and potassium clavulanate and one or more pharmaceutically acceptable inert excipients can be made.

The agglomerates, prepared according to the present invention, are suitable to prepare oral dosage forms such as tablets, capsules, syrups or sachets, dry instant or ready to use in multiple or single dose form. According to another embodiment of the invention, the oral dosage form, comprising agglomerates or granules of amoxicillin with or without one or more excipients can also contain a β-lactamase inhibitor such as potassium clavulanate, preferably in the agglomerated form. Said agglomerates can also be used in Dose Sipping devices.

Detailed description of the invention

The present invention provides economically interesting agglomerates in crystalline form of a ß-lactam compound. The ß-lactam compounds are for instance clavulanic acid but one can also think of amoxicillin or ampicillin. The compound can be in the salt form, such as amine or alkaline metal salt. Preferably, agglomerates of potassium clavulanate are produced.

The agglomerates of said invention have an average particle size between about 1 μm and 1500 μm, preferably between about 500 μm and 1500 μm, more preferably between 800 μm and 1200 μm, or between 1 μm and 300 μm, preferably between 1 μm and 200 μm.

Furthermore, said agglomerates are preferably substantially free from non-agglomerated ß-lactam crystals, as for instance in the needle form. By substantially free from non-agglomerated crystals is meant that the agglomerates have a weight percentage between 0-10% of non-agglomerates.

A process for the preparation of the agglomerates, wherein one or more ß-lactam compounds with or without excipients are used, consists of a crystallisation procedure to build up agglomerates. The process comprises mixing together a solution or suspension of one or more ß-lactam compounds

corresponding to the agglomerates to be produced in a solvent or in a mixture of solvents with one or more anti-solvents under stirring. The combination of solvent and anti-solvent can result in an emulsion. In the solvent or anti-solvent an amount of water should be present, for instance in an amount of 0.05 to 10%. Thereafter, the agglomerates are filtered off, washed and dried. The agglomerates, thus produced in high yield, maintain the quality criteria set and are highly suitable for further processing. For the present application, a anti-solvent is defined as a liquid in which the ß-lactam compound does not dissolve or dissolves only poorly.

More in detail, the ß-lactam compound, for instance potassium clavulanate, is dissolved or suspended in an appropriate solvent or a mixture of (partly) miscible solvents, such as water, alcohols, like ethanol, methanol, 1-propanol, 2-butanol, 2-methyl-propanol, ketones, like acetone, methylethylketone, methylisobutylketone, or an ester, like methyl acetate, ethyl acetate, butyl acetate, with at least a small amount of water present. Sometimes an emulsion is formed during the agglomeration process. Optionally, the pH of the solution is adjusted to about neutral, namely to pH 5.0-7.5 by adding an acid, as for instance acetic acid or ethylhexanoic acid. The way of dissolution will be known to those skilled in the art and will depend on the stability of the ß-lactam compound in the solvent or in a mixture of solvents. In case water is used as the only solvent for the dissolution of potassium clavulanate, residence time and temperature should be as low as possible and a technique such as in-line mixing, for example a static mixer, can be attractive. If for example acetone is present, a residence time of several hours might be acceptable.

The ß-lactam compound, for example potassium clavulanate, present in the solvent dissolved or in suspension or in both forms, is contacted with a anti-solvent such as ketone, like acetone, methylethylketone, methylisobutylketone, or an ester, such as methyl acetate, ethyl acetate, butyl acetate or a mixture thereof, or an alcohol such as 1-propanol, 2-butanol, 2-methyl-propanol optionally containing a solvent for the ß-lactam compound,

such as water or an alcohol, like methanol or ethanol for potassium clavulanate. The overall weight ratio of the solution containing the ß-lactam compound to the anti-solvent depends on the combination of solvents and on the desired agglomerate diameter, but generally lies within 0.05-10%. Also, it is possible to adjust this ratio by adding some solvent to the crystalliser before or during the process. This ratio will influence the average diameter of the agglomerates: the higher the relative volume of the solvent, the larger the agglomerates will be.

Several methods of mixing can be applied and will be known to those skilled in the art. For example, the solution of the ß-lactam compound, for instance a potassium clavulanate solution and the anti-solvent can be added simultaneously to the crystalliser or the solution of the ß-lactam compound, for instance a potassium clavulanate solution can be added to the anti-solvent or the anti-solvent can be added to the solution of the ß-lactam compound, for instance a potassium clavulanate solution. The temperature should be kept below 50°C. The use of seeding material can also be advantageous to enhance the agglomeration process.

The method of contacting the potassium clavulanate containing solution and the anti-solvent can be controlled *via* specific equipment, such as spray nozzles or capillaries. This contacting can occur in a vessel or in line or in a recycling loop over the vessel. It is also possible to first form droplets of solution of a certain diameter, after which the droplets are contacted with the anti-solvent.

Parameters such as the amount of nozzles, their diameter, the flow through the nozzles and the rotational speed of the mixer can be used to control the average particle size and density. In this way, several grades of agglomerates can be produced, with different physical properties.

The method of agitation is determined by the desired agglomeration size of the ß-lactam compound. In case of relatively large agglomerates (order of magnitude of 1000 μm), the agitation should be moderate. For example a common turbine agitator or pitched blade agitator can be used. Here, the

general scales up parameters for agitation apply: the diameter of the blades versus the diameter of the vessel should be between 0.2-0.9, preferably between 0.2-0.5, depending on the type of agitator used. The rotational speed (and thus shear), tip velocity, the size of the nozzle sprayer and power input determine the agglomerate size and density and can be used as control parameters. In case the desired agglomerate diameter is small, for example 50-100 μm, high speed agitators, such as toothed disks or rotor-stator mixers with multiple stage mixing/shearing action can be used. It is also possible to use in-line high shear mixers, with the advantage of short residence times. If needed, a recycle loop can be applied over such an in-line system. Another possibility is to combine a moderate shear mixer with a high shear mixer or a mill. For example, agglomerates with a diameter of the order of a magnitude of 1000 μm can be deagglomerated during the crystallisation using a high shear mixer, which is situated in the same crystalliser (such as mounted in the bottom) or as a separate unit after the crystalliser. Also, for example a colloid mill can be placed after the crystalliser for the same purpose. Moreover, the simultaneous crystallisation/agglomeration technique can be combined using ultrasonic crystallisation. This technique has been described for instance in *Pharmaceutical Technology Europe*, 9(9), 78 (1997). In this way different grades concerning particle size distribution, density, porosity and flowability can be easily achieved.

Generally, the residence time in the crystalliser and/or deagglomerator is determined by the desired average diameter of the agglomerates. For purposes of precipitation/crystallisation, long ageing times are not needed, as the crystals are formed immediately after contact with the anti-solvent. For agglomeration and deagglomeration, however, a certain minimum and maximum residence time will be valid, depending on parameters such as mixing time and volume of the vessel.

One of the embodiments of the invention is to have the excipients included in the agglomerates by addition of the same before, after or during the precipitation and/or agglomeration, such as cellulose, preferably

microcrystalline cellulose, more preferably with a water activity < 0.2 at 25°C, most preferably Avicel® PH112. Also, amorphous silica (Syloid®) or colloidal silicon dioxide (Aerosil®) can be used as excipient. All methods of mixing are possible: for example the excipient can be added before, simultaneously or after the addition of the ß-lactam compound solution or (partly) suspension to the crystalliser. The excipients can be added as dry matter, suspended or dissolved in a solvent, preferably one of the solvents (or a mixture thereof) which is already used in the agglomeration process. An extra advantage of the addition of such excipients is the positive influence on the agglomeration formation, as they can act as some kind of seeding material.

Another embodiment of the present invention is that the crystallisation and agglomeration can occur in the presence of another active ß-lactam ingredient, for example amoxicillin trihydrate besides potassium clavulanate. The amoxicillin can either be added as a solution or suspension leading to co-crystallisation, similar to the agglomeration in the presence of excipients.

The agglomerates of the present invention are not of the rosette type: they consist of small crystals clustered together in a random order (see the Figure). Depending on the method of agitation, method of addition and amount of water, the agglomerate size can easily be adjusted between about 1 and 1500 μm and also relatively small particles as with an average size of 100 μm or relatively large particles with an average size of 1000 μm may be prepared. Compared to, for example, dry compaction, the amount of fines that either must be discharged of or that must be recycled, is small. The agglomerates can easily be separated by for example, filtration or centrifugation and subsequently dried using conventional methods such as tumbling drying. It is also possible to include a classification process. For example, agglomerates of the desired size can be selectively removed from the crystalliser using gravity and/or a sieve. Fines or large particles which can be removed by sieving as well, can be recycled, either by addition in suspension or solution to the next batch.

If necessary, pH-adjustment in order to adapt the pH of the end product can be achieved by adding an acid or base to the solution or the anti-solvent before contacting the streams of solvents containing the ß–lactam compound and the anti-solvent. Also, acid or base can be added during the precipitation/crystallisation/ agglomeration process or even after the process.

Surprisingly, the process of the present invention produces agglomerates with a high bulk density, an improved flowability and less compressibility, which can be regulated. For example, potassium clavulanate agglomerates produced can have a loose bulk density between about 0.20 and 0.60 and a tapped bulk density between about 0.50 and 0.90 g/ml and a compressibility between about 10 and 40%.

Due to the excellent flowability of the agglomerates prepared using the above method, they can be used for, for example, direct compression of tablets without the need for further pre-granulation. Moreover, due to the decreased surface area of the agglomerates, the degradation caused by chemical reactions on the surface (e.g. with water) may be reduced. The level of impurities in the agglomerates is also equal to or even lower than in case of conventional needles type crystals. As the bulk density increases significantly, large advantages can be achieved in the transportation as well as in the tabletting process: the final tablet volume can decrease significantly when using agglomerates compared to using needles.

The energy consumption of the present process is low, as the crystallisation process which is commonly present in the down stream process of pharmaceuticals can be combined with the agglomeration process. Moreover, it is possible to combine the usual operations comprising purification and separation by precipitation or crystallisation, agglomeration and deagglomeration, classification and blending with e.g. excipients in one unit. The temperatures can be kept below 50°C during the complete agglomeration process, excipients-free agglomerates can be produced and handling of dry solids before the granulation does not occur, which is an important advantage in case of hygroscopic materials. The solvents needed

for the agglomeration can easily be recycled, possibly without the need for purification. Moreover, the possibility to make pure agglomerates of an unstable and hygroscopic product such as potassium clavulanate is highly attractive.

The agglomerates of the present invention can be used for all formulations to produce chew, swallow, disperse, effervescent or normal tablets of all sizes, forms and weights, also to fill hard gelatine capsules and to formulate dry syrups and for administering drugs with the help of a dose sipping device. These agglomerates can also be used, for instance, in a pharmaceutical composition as a tablet of amoxicillin trihydrate produced from agglomerates of amoxicillin trihydrate and potassium clavulanate. For the preparation of sterile agglomerates, the solution of the ß-lactam compounds, solvent and anti-solvent are sterilely filtered prior to crystallisation/agglomeration. Also, the sterile agglomerates substantially free of non-agglomerates, form another aspect of the present invention.

The invention will now be described with reference to the following Examples, which are not to be constructed as being limiting on the invention, and are provided purely for illustrative purposes.

Example 1

Preparation of agglomerates of potassium clavulanate (batch process).

In a 5-litre flask equipped with a mechanical stirrer, a thermometer and inlet for nitrogen, 4 litres of acetone were placed. A solution of potassium clavulanate (60 g.) in a mixture of water/acetone (120 g, 1:1 w/w) was added in 30 min at 20°C under stirring.

The solid material was filtered off and dried in vacuum at 30°C during 2-3 hours to give agglomerates of potassium clavulanate with an average diameter in the range of 100-1000 μm and a yield of 98% .

Example 2

Preparation of agglomerates of potassium clavulanate (semi-continuous process).

In a 2-litre flask equipped with a mechanical stirrer, a thermometer and inlet for nitrogen, acetone (1000 ml) and water (10 ml) were placed. Simultaneously a solution of potassium clavulanate (60 g) in a mixture of water/acetone (120 g, 1:1 w/w) and acetone (4000 ml) was added in about one hour, while agitating.

During the addition the content of the vessel was kept at about 1800 ml by periodically removing suspension through an outlet.Thereafter, the solid material was filtered off, washed with dry acetone and dried in vacuum at 30°C during 2-3 hours to yield potassium clavulanate agglomerates with an average diameter in the range of 500-1500 μm.

Example 3

Preparation of agglomerates of potassium clavulanate by using a turbine stirrer without baffles in the reaction vessel.

Acetone (300 ml) and water (3 ml) were placed in a glass cylinder (100 mm in diameter, 150 mm height) equipped with a turbine stirrer (40 mm diameter), a two dropping funnel and a nitrogen inlet tube. Under stirring (900 rpm) simultaneously a solution of potassium clavulanate (30 g) in a water/acetone mixture (60 g, 1:1 w/w) and acetone (2000 ml) were added.

During the addition, the contents of the vessel were kept at about 900 ml by removing a part of the contents with the help of an outlet. After the completion of the additions, the solid material was filtered off, washed with dry acetone and dried in vacuum at 30°C. Agglomerates of potassium clavulanate with an average particle diameter of 1000 μm were obtained in 98% yield.

Example 4

Preparation of agglomerates of potassium clavulanate by using turbine stirrer with baffles in the reaction vessel.

The experiment was repeated as described in Example 3, but using a vessel with four baffles with a width of 10 mm. Potassium clavulanate agglomerates with an average diameter in the range of 500-1000 μm were obtained.

Example 5

Preparation of agglomerates of potassium clavulanate by using a Ultra-Turrax mixer.

Acetone (500 ml) and water (5 ml) were placed in an one litre 4-necked round-bottom flask equipped with a thermometer, Ultra-Turrax mixer (type T25 and shaft S25N-18G), two dropping funnels and a nitrogen inlet tube.

Under mixing (8000 rev/min) simultaneously a solution of potassium clavulanate (30 g.) in a water/acetone mixture (60 g. 1:1 w/w) and acetone (2000 ml) was added in one hour at 15-20°C. During the addition, the contents of the vessel were kept between 700 and 800 ml by removing a part of the content with the help of an outlet.

After the completion of the additions, the solid material was filtered off, washed with acetone and dried in vacuum at 30°C. Agglomerates of potassium clavulanate with an average diameter in range of 50-250 μm were obtained.

Example 6

Preparation of agglomerates of potassium clavulanate by using Silverson L4RT mixer.

The experiment was repeated as described in Example 5, but using a rotor-stator type high shear mixer (Silverson mixer with emulsion screen, i.e. a screen with spherical pores of about 1.5 mm) at 3000 rev/min.

Agglomerates of potassium clavulanate with an average diameter in the range of 10-200 μm were obtained.

Example 7

Preparation of agglomerates of potassium clavulanate in ethyl acetate.

Ethylacetate (400 ml) and water (1 ml) were placed in a glass cylinder (100 mm in diameter, 150 mm height) equipped with a turbine stirrer (40 mm diameter), a two dropping funnel and a nitrogen inlet tube. Under stirring (900 rpm) at the same time a solution of potassium clavulanate (10 g) in water (10 ml) and ethyl acetate (600 ml) were added.

After the completion of the additions the solid was filtered off, washed with dry ethyl acetate and dried in vacuum at 30°C to give agglomerates with an average diameter in the range of 500-1500 μm.

Example 8

Comparison of agglomerates and needles of potassium clavulanate, optionally mixed with Avicel PH112.

The agglomerates of potassium clavulanate were prepared as described in Example 6, but using a Silverson mixer with general purpose disintegrating screen, i.e. a screen with square holes with a diameter of about 2.5 mm. In a 2- litre flask equipped with the Silverson mixer, a thermometer and inlet for nitrogen acetone (1000 ml) and water (10 ml) were placed. Under mixing (3400 rev/min) simultaneously a solution of potassium clavulanate (120 g) in a mixture of water/acetone (240 g, 1:1 w/w) and acetone (8000 ml) were added at 15-20°C. During the addition the contents of the vessel was kept at about 1800 ml with an outlet. After completion of the additions the solid was

filtered off, washed with acetone and dried in vacuum at 30°C during 2-3 hours to give agglomerates with an average diameter in the range of 40-200 μm.

Needles of potassium clavulanate were prepared by suspending diclavulanate salt of bis(2-dimethylaminoethyl) ether (100 g) in acetone (3350 ml) and water (50 ml). Under stirring a solution of potassium 2-ethylhexanoate (1450 ml, 0.34 M) in acetone at 5-10°C was added. After 1 hour stirring the mixture was filtered off, washed with dry acetone and dried in vacuum during 18 hours at room temperature to give 81.2 g of potassium clavulanate needles.

A comparison of physical properties of potassium clavulanate in agglomerated and needle form, optionally mixed with Avicel PH112 in a ratio of 70 : 30 w/w% have been described in Table 1.

Table 1: Comparison of physical properties of potassium clavulanate in agglomerated and needle form, optionally mixed with Avicel PH112

Material	Loose bulk density	Tapped bulk density	Compressibility	Particle size distribution
Agglomerates of potassium clavulanate	0.49g/ml	0.68g/ml	28%	between 1 and 200μm
Needles of Potassium clavulanate	0.18g/ml	0.36g/ml	50%	between 5 and 75μm
Agglomerates of potassium clavulanate mixed with Avicel PH112	0.43g/ml	0.61g/ml	29%	Not determined
Needles of potassium clavulanate mixed with Avicel PH112	0.20g/ml	0.40g/ml	50%	Not determined

Example 9

Preparation of agglomerates of potassium clavulanate in acetone/water at a speed of the agitator of 3000 RPM.

A solution of potassium clavulanate was made by dissolving circa 5 kg of potassium clavulanate in 10 l aqueous acetone (acetone:water = 50:50 w/w). This solution, which was kept at 5°C was pumped through a 0.9 mm nozzle to a crystalliser equipped with a high shear mixer and containing 50 l of acetone. Simultaneously, acetone was added to the crystalliser with a volume ratio compared to the solution of circa 21. During the process, the rotational speed of the agitator was 3000 RPM and the temperature was circa 15°C. The agglomerated suspension was removed continuously from the crystalliser, centrifuged, washed with dry acetone and dried in vacuum at 30°C. In this way, agglomerates such as shown on the Figure were produced with a loose bulk density of 0.22 g/ml, a tapped bulk density of 0.30 g/ml and a compressibility of 27%. The particle size distribution is given in Table 2 and a photo made by an Electron-microscope of potassium clavulanate is shown in the Figure.

Table 2: Particle size distribution [volume %]

<75 µm	75-150 µm	150-250 µm	250-500 µm	500-710 µm	> 710 µm
46.3	43.3	8	1	0.2	0.1

Example 10

Influence of the agitator speed during agglomeration on the physical properties of the agglomerates.

A solution of potassium clavulanate was made by dissolving circa 10 kg of potassium clavulanate in 20 l aqueous acetone (acetone:water = 50:50 w/w). This solution, which was kept at 5°C was pumped through a 2.5 mm nozzle to a crystalliser equipped with a high shear mixer and containing 40 l of acetone. Simultaneously, acetone was added to the crystalliser with a volume ratio compared to the solution of circa 22. During the process, the rotational speed of the agitator was increased from 1000 RPM to 2000 RPM and the temperature was circa 15°C. Continuously, the suspension was removed from

the crystalliser using a pump. The two agglomerated suspensions made were centrifuged, washed with dry acetone and dried in vacuum at 30°C. The physical properties can be seen in Table 3.

Table 3: Physical properties: particle size distribution [volume %]

	Loose bulk density [g/ml]	Tapped bulk density [g/ml]	Compressibility [%]	<75 µm	75-150 µm	150-250 µm	250-500 µm	500-710 µm	> 710 µm
1000 RPM	0.39	0.44	11	5.1	6.5	20.7	60.8	6.1	0.2
2000 RPM	0.42	0.47	11	1.8	2.4	9.5	57.3	27	1.5

Example 11

Influence of the flow upon addition to crystalliser on the physical properties of the agglomerates.

Two experiments were performed in which all parameters were kept constant, except the flows of the solution and acetone to the crystalliser. In both experiments, a solution of potassium clavulanate was made by dissolving circa 5 kg of potassium clavulanate in 10 l aqueous acetone (acetone:water = 50:50 w/w). This solution, which was kept at 5°C was pumped through a 0.9 mm nozzle to a crystalliser equipped with a high shear mixer and containing 30 l of acetone. Simultaneously, acetone was added to the crystalliser with a volume ratio compared to the solution of circa 21. During the process, the rotational speed of the agitator was 3000 and the temperature was circa 15°C. In the first experiment, the solution flow was 15 l/h and the acetone flow was 312 l/h. In the second experiment, the flows were decreased by a factor 2. Continuously, the suspension was removed form the crystalliser using a pump. The two agglomerated suspensions made were centrifuged, washed with dry acetone and dried in vacuum at 30°C. The physical properties can be seen in Table 4.

Table 4: Physical properties: Particle size distribution [volume %]

	Loose bulk density [g/ml]	Tapped bulk density [g/ml]	Compressibility [%]	<75 µm	75-150 µm	150-250 µm	250-500 µm	500-710 µm	> 710 µm
High flow	0.27	0.36	25	48.7	41.2	9.3	0.3	0	0
Low flow	0.35	0.44	20	48.8	50.4	1.1	0.6	0.4	0

Example 12

Influence of the nozzle diameter through which the potassium clavulanate solution is pumped on the physical properties of the agglomerates.

Two experiments were performed in which all parameters were kept constant, except the diameter of the nozzle through which the potassium clavulanate solution is added to the crystalliser. In both experiments, a solution of potassium clavulanate was made by dissolving circa 5 kg of potassium clavulanate in 10 l aqueous acetone (acetone:water= 50:50 w/w). This solution, which was kept at 5°C, was pumped through either a 0.9 mm or 1.2 mm nozzle to a crystalliser equipped with a high shear mixer and containing 50 l of acetone. Simultaneously, acetone was added to the crystalliser with a volume ratio compared to the solution of circa 21. During the process, the rotational speed of the agitator was 3000 and the temperature was circa 15°C. Continuously, the suspension was removed from the crystalliser using a pump. The two agglomerated suspensions made were centrifuged, washed with dry acetone and dried in vacuum at 30°C. The physical properties can be seen in Table 5.

Table 5: Physical properties: particle size distribution [volume %]

Nozzle diameter	Loose bulk density [g/ml]	Tapped bulk density [g/ml]	Compressibility [%]	<75 µm	75-150 µm	150-250 µm	250-500 µm	500-710 µm	> 710 µm
0.9 mm	0.22	0.3	0.27	46.3	43.3	8	1	0.2	0.1
1.2 mm	0.36	0.44	0.18	15.9	50.6	31.3	1.9	0	0.3

CLAIMS

1. Agglomerates in crystalline form comprising one or more ß-lactam compounds, wherein at least one ß-lactam compound has a high water affinity, and optionally containing one or more excipients, with the proviso that the rosette-like crystalline form of potassium clavulanate is excluded.

2. Agglomerates according to claim 1, wherein the agglomerates are substantially free from non-agglomerated ß-lactam crystals.

3. Agglomerates according to claim 1 or 2, wherein at least one ß-lactam compound is clavulanic acid.

4. Agglomerates according to any one of the claims 1-3, wherein the ß-lactam compound is potassium clavulanate.

5. Agglomerates according to claim 4, consisting of only potassium clavulanate.

6. Agglomerates according to claim 4 further comprising amoxicillin.

7. Agglomerates according to anyone of the claims 1-4 or 6, wherein the excipients are microcrystalline cellulose, preferably Avicel®, or silica, preferably Syloid® or Aerosil®.

8. Agglomerates according to anyone of the claims 1-7, wherein the agglomerates have an average particle size between about 1 μm and 1500 μm, preferably between about 500 μm and 1500 μm, more preferably between 800 μm and 1200 μm, or preferably between 1 μm and 300 μm, more preferably between 1 μm and 200 μm.

9. Agglomerates according to anyone of the claims 1-8 in sterile form.

10. A process for the preparation of crystallised agglomerates as defined in anyone of the claims 1-9, wherein the agglomerates are produced in a liquid phase by applying stirring devices.

11. A process according to claim 10, wherein the liquid phase comprises a solution or suspension of at least one corresponding ß-lactam compound in a solvent or in a mixture of solvents together with one or more anti-solvents.

12. A process according to claim 11, wherein the ratio of the weight of the solution containing ß-lactam compound to the anti-solvent is about 0.05 to 10 wt.%.

13. A process according to claim 11 or 12, wherein the solvent is selected from the group consisting of water, alcohol, ketone and ester or a mixture thereof, whereby water is present.

14. A process according to anyone of the claims 10-13, wherein the anti-solvent is a ketone, like acetone, methylethylketone, methylisobutylketone or an ester, like methyl acetate, ethyl acetate, isopropyl acetate, butyl acetate or an alcohol, like 1-propanol, 1-butanol, 2-butanol, 2-methyl-1-propanol or a mixture of these solvents, optionally containing water.

15. A process according to anyone of the claims 10-14, wherein one or more stirring devices are used to crystallise, agglomerate and/or deagglomerate the ß-lactam compound and optionally classification and blending with excipients and/or another ß-lactam compound in a batch or continuous operation, in one or more units.

16. A process according to claim 15, wherein the process is performed by applying stirring devices in one or more vessels, in-line mixers or a combination thereof.

17. A process according to claim 15 or 16, wherein a high shear mixer is used as stirring device.

18. A process according to anyone of the claims 10-17, characterised by the preparation of agglomerates with various particle sizes, by further using a combination and permutation of different stirring devices and their speed, the type and amount of the solvents used and the way of mixing of one or more solvents and anti-solvents.

19. A process according to claim 18, characterised by the preparation of agglomerates with various particle sizes, by further using a nozzle-sprayer for the solution.

20. A process according to any one of the claims 10-19, characterised by dissolving one or more corresponding ß-lactams in a solvent, adjusting the pH to about neutral and mixing with the anti-solvent.

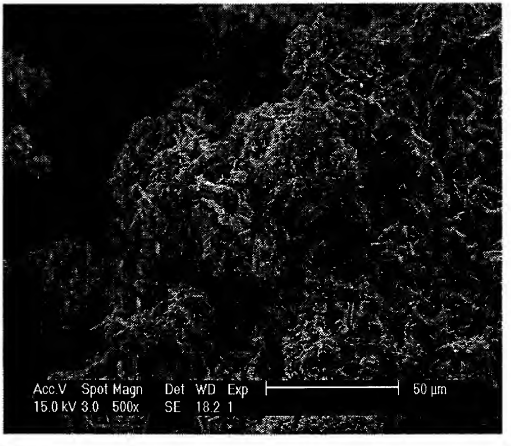
21. A pharmaceutical formulation comprising the agglomerates of anyone of the claims 1-9 and one or more pharmaceutical acceptable excipients.

22. A pharmaceutical formulation comprising amoxicillin, preferably amoxicillin trihydrate and the crystalline agglomerates of potassium clavulanate as defined in claim 5, and optionally one or more pharmaceutically acceptable inert excipients.

23. A pharmaceutical formulation, comprising a mixture of amoxicillin trihydrate and crystalline agglomerates of potassium clavulanate and one or more pharmaceutically acceptable inert excipients as defined in claim 4.

24. Pharmaceutical dosage form comprising a pharmaceutical formulation of anyone of the claims 21-23.

Figure



PATENT
Docket No. 24615_____

DECLARATION FOR [UTILITY/DESIGN] PATENT APPLICATION

AS A BELOW-NAMED INVENTOR, I HEREBY DECLARE THAT:

My residence, post office address, and citizenship are as stated below next to my name.

I believe I am the original, first and joint] inventor of the subject matter which is claimed and for which a patent is sought on the invention entitled: AGGLOMERATES BY CRYSTALLISATION , the specification of which is attached hereto unless the following box is checked:

☒ was filed on PCT International Application No. PCT/EP00/012917 and was amended on * (if applicable).

I HEREBY STATE THAT I HAVE REVIEWED AND UNDERSTAND THE CONTENTS OF THE ABOVE-IDENTIFIED SPECIFICATION, INCLUDING THE CLAIMS, AS AMENDED BY ANY AMENDMENT REFERRED TO ABOVE.

I acknowledge the duty to disclose information, which is material to the patentability as defined in 37 C.F.R. § 1.56.

I hereby claim foreign priority benefits under 35 U.S.C. § 119(a)-(d) or § 365(b) of any foreign application(s) for patent or inventor's certificate, or § 365(a) of any PCT International application which designated at least one country other than the United States listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or PCT International application having a filing date before that of the application on which priority is claimed:

Application No.	Country	Date of Filing (day/month/year)	Priority Claimed?
99201034.8	EP/NL	01/04/1999	☒Yes ☐No

I hereby claim benefit under 35 U.S.C. § 119(e) of any United States provisional application(s) listed below:

Application Serial No.	Filing Date
*	

I hereby claim the benefit under 35 U.S.C. § 120 of any United States application(s), or § 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. § 112, I acknowledge the duty to disclose information which is material to patentability as defined in 37 C.F.R. § 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application.

Application Serial No.	Filing Date	Status
PCT/EP00/02917	03/04/2000	☐Patented ☐Pending ☐Abandoned

I hereby appoint the following attorneys and agents to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith:

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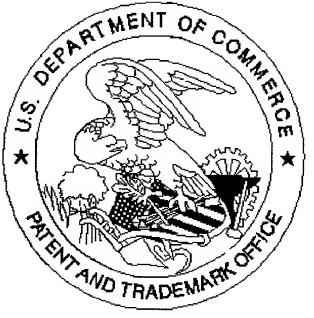

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